IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

In re application of: Bell *et al.* | Confirmation No.: 4773

Appl. No. 09/664,444 | Art Unit: 1645

Filed: September 18, 2000 | Examiner: R. Zeman

For: **ONCOLYTIC VIRUS** | Atty. Docket: 18003

Cust. No. 31976

January 14, 2009

Pre-Appeal Brief Request For Review

MAIL STOP AF
Commissioner for Patents
P.O. Box 1450
Alexandria, VA 22313-1450

Sir:

Applicants request review of the final rejection in the above identified application. No amendments are filed with this request. This Pre-Appeal Brief Request for Review is filed with a Notice of Appeal.

Remarks begin on page 2. As required, Applicants have provided no more than 5 pages (pages 2-6) of arguments.

Status of Application

Claims 1, 6-13, 19, 24-37 and 64-80 are pending in the application. Claims 1, 6-13, 19, 24-37, 64-77 and 79-80 have been finally rejected under 35 U.S.C. § 112, first paragraph, as not enabled. (July 16, 2008, Office Action, page 5.) Claims 27-31 and 73-77 have been finally rejected under 35 U.S.C. § 112, first paragraph, for failing to meet the biological deposit requirements. (July 16, 2008, Office Action, page 3.)

Remarks Supporting Request For Review

I. Claimed Invention is Enabled

The Examiner has finally rejected claims 1, 6-13, 19, 24-37, 64-77 and 79-80 under 35 U.S.C. § 112, first paragraph, as not enabled. (July 16, 2008, Office Action, page 5.)

The Examiner's rejection is deficient and legally insufficient in that, *inter alia*, (A) the rejection focuses on whether Applicants' specification has enabled claims directed to treating cancer and/or efficacy in a human[1] and (B) Applicants have demonstrated that upon review of Applicants' specification, one skilled in the art, at the time of the invention, would have been able to practice the claimed invention without undue experimentation.

A. Improper Enablement Standard

Even though the practice of the claimed invention may result in a therapeutic benefit, the subject matter of the claims relates to "reducing the viability of a tumor cell". The present claims do not recite or require any "efficacy" or "therapeutic effect". However, the Examiner inappropriately reads the requirement for efficacy and/or therapeutic effect into the claims. For example, the Examiner states,

> contrary to applicant's assertion [that there is no limitation to treat cancer], the reduction in the viability of a tumor cell in the context of a living being . . . constitutes a therapeutic response . . . . Consequently, clinical response is pertinent with regard to the enablement of the instant claims.

(July 16, 2008, Office Action, page 6.) On the contrary, whether or not a clinical response can be shown or predicted is not pertinent for meeting the enablement requirement with regards to the subject matter of the claimed invention, since the claims do not recite any limitations directly related to a therapeutic reduction of tumor cell viability or clinical response.[1] What is pertinent is whether one skilled in the art can make and use the invention commensurate with the scope of the claims, *i.e.* to reduce the viability of a hematopoietic tumor cell with administration of a vesicular stomatitis virus (VSV), commensurate with the claims.

In the initial paragraph of the enablement rejection (July 16, 2008, Office Action, page 5), the Examiner refers to reducing the viability of a tumor cell, but then goes on to focus on arguments and documents allegedly showing that certain models and/or experiments do not correlate with efficacy or treatment in humans. For example, the Examiner states,

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[1] For clarity, Applicants believe that, if presented, similar claims to treating hematopoietic tumor cells are enabled by the present application.

> Gura . . . teach that xenographs are not good models for determining the efficacy of a treatment modality . . . . Gura illustrates the lack of correlation between efficacy in xenograft model systems and in vivo efficacy in humans.

(July 16, 2008, Office Action, page 12, underlining added.)

Additionally, Applicants' Reply of April 7, 2008 (pages 16-17) referred the Examiner to *Ex parte* Saito and Zhao[2] and *Ex parte* Boutin[3]. The claims in both *Ex parte Saito and Zhao* and *Ex parte Boutin* require expression of a gene but do not require a therapeutic result. Both of these decisions stand for the proposition that to satisfy the enablement requirement, all that is required, based on the respective claims, is the expression of the transgene and not a therapeutic benefit. This is similar to the present application in that the claims require reduction of the viability of a hematopoietic tumor cell, but not a therapeutic benefit. The Examiner has provided no evidence that one skilled in the art would not have been able to reduce the viability of a hematopoietic tumor cell, *in vitro* or *in vivo*.

Additionally, Applicants also referred the Examiner to *Ex parte Ayishi*,[4] where the BPAI also reversed the Examiner's enablement rejection. This case is similar to the present case in that the claims do not specifically recite or require a therapeutic effect, but recite methods that may encompass methods achieving a clinically effective therapeutic response. A very pertinent quote from *Ex parte Ayisi* is recited and discussed in Applicants' Reply of Sept. 16, 2008 at pages 13-15. In brief, the claims in *Ex parte Ayisi* refer to a method comprising contacting a virus-infected cell with an extract from Ocimum gratissimum in an amount effective to inhibit cytopathic effects of the virus in the cell, whereas the present claims refer to methods of reducing the viability of a tumor cell, comprising administering to the tumor cell a VSV.

B. Applicants Have Demonstrated That Claims Are Enabled.

The Examiner has not expressed specific reasons why one skilled in the art, upon review of Applicants' specification would not have expected the claimed methods to result in the reduction of the viability of a tumor cell. At most, some of the references cited by the Examiner may suggest that some drug candidates with positive results in a xenograft model are not later approved or used as drugs in people. However, a drug candidate may fail to become an approved drug for various reasons including (i) the reduction in tumor cell viability may not

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[2] Appeal No. 2005-1442 before the Board of Patent Appeals and Interferences (BPAI), not binding precedent of the Board; Appendix B of April 7, 2008 Reply.

[3] Appeal No. 2006-1879 before the BPAI, not binding precedent of the Board; Appendix C of April 7, 2008 Reply.

[4] Appeal No. 2006-1608 before the BPAI, not binding precedent of the Board; Appendix A of September 16, 2008 Reply and discussed at pages 13-15 of Applicants' Reply of September 16, 2008.

meet a justifiable or predetermined level, (ii) the general toxicity may be too great, (iii) the therapeutic benefit does not justify the cost and/or (iv) the therapeutic results are not equivalent to or better than a standard of care. Therefore, drug candidates can fail to be approved treatments even though they are shown to reduce the viability of tumor cells in a patient. None of the references cited by the Examiner demonstrate or suggest that, upon review of the present specification, one skilled in the art would not have been able to reduce the viability of a hematopoietic tumor cell *in vitro* or *in vivo* using the claimed methods.

Additionally, Applicants have previously provided various reasons and evidence showing that one skilled in the art would have expected the claimed methods to result in the reduction of the viability of a tumor cell, even *in vivo* or in an immunocompetent animal.[5] For example, Applicants' previous Replies have shown that numerous hematopoietic tumor types, are susceptible to VSV infection.[6] This represented a wide range of tumor cell types and included *in vitro* testing, testing of human patient samples and orthotopic models. This demonstrated that the viability of hematopoietic tumor cells, in general, are reduced upon administration of a VSV.

Furthermore, the specification teaches very specific characteristics for which one skilled in the art can, without undue experimentation, screen a particular hematopoietic tumor cell type to confirm its sensitivity to VSV (see *e.g.*, page, 4 lines 8-22; page 11, lines 21-27; page 12, line 7 to page 16, line 22; and Example 1).[7]

Additionally, Applicants refer to the Examiner's statement made during the prosecution of Applicants' related U.S. Patent Application No. 11/685,483 ('483 application), which is a continuation of 10/743,639 which is a divisional of the present application.[8] Claim 1 of the '483 application is similar to claim 1 of the present application with the main difference being the type of tumor cell recited, carcinoma versus hematopoietic. In an obviousness rejection of, *inter alia*, claim 1 of the '483 application, the Examiner stated that "the use of VSV as a cancer treatment is well known in the art yielding predictable results". (April 10, 2008, Office Action, page 21, for the '483 application.) Something well known in the art yielding predictable results is clearly

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[5] For example, see Applicants' Replies of (i) April 7, 2008, pages 14-18 and Appendices B & C; and (ii) August 2, 2007, pages 11-22.

[6] For example, see Applicants' Replies of (i) August 2, 2007, pages 15-17 and (ii) November 24, 2004, pages 4-6 and Tables A & B.

[7] For clarity, with the exception of claims 19 and 71, Applicants' claimed invention is not limited to reducing the viability of tumor cells with these characteristics.

[8] These statements were previously discussed in Applicants' Reply of September 16, 2008 at pages 12-13.

enabled.

In view of the above, Applicants respectfully request the Examiner to reconsider and withdraw the enablement rejection of claims 1, 6-13, 19, 24-37, 64-77 and 79-80.

II. A Biological Deposit Is Not Required for Enablement

The Examiner has finally rejected claims 27-31 and 73-77 under 35 U.S.C. 112, first paragraph, "for failing to meet the biological deposit requirements . . . . The deposit of biological organisms is considered by the Examiner to be necessary for the enablement of the current invention". (July 16, 2008, Office Action, pages 3-4.)

> The Manual of Patent Examining Procedure (MPEP) states,
> [i]n an application where the invention required access to specific biological material, an applicant could show that the biological material is accessible because it is known and readily available to the public. The concepts of "known and readily available" are considered to reflect a level of public accessibility to a necessary component of an invention disclosure that is consistent with an ability to make and use the invention . . . . Unless there is a reasonable basis to believe that the biological material will cease to be available during the enforceable life of the patent, current availability would satisfy the requirement . . . . **If an applicant has adequately established that a biological material is known and readily available, the Office will accept that showing.**

(MPEP § 2404.01 (eighth edition, September 2007); underlining and bolding added.)

The Examiner's rejection is deficient and legally insufficient in that, *inter alia*, the Examiner maintains this rejection in spite of Applicants submitting evidence establishing that the claimed VSV strains are known and readily available to the public. Additionally, the Examiner has not, as required, put forth any reasonable basis to believe that the biological material will cease to be available during the enforceable life of the patent.

Applicants have previously shown that the biological material is readily available by presenting a review of the scientific literature indicating that a variety of researchers have had access to the VSV strains of claims 27-31 and 73-77.[9] To further show that the claimed biological materials are readily available, Applicants also submitted examples of the policies for most of the journals which published on the claimed VSV strains.[10] These policies indicate that the authors agree to make biological materials available to the scientific community. Therefore, the claimed VSV strains are generally available to researchers in the field and a deposit under the

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[9] For example, see Applicants' Reply of April 7, 2008, page 12.

[10] For example, see Applicants' Reply of April 7, 2008, page 13 and Appendix A.

terms of the Budapest Treaty is not necessary to meet the enablement requirement.

As discussed above, the MPEP states that if an applicant has adequately established that a biological material is known and readily available, the Office will accept that showing. Applicants have made this showing and the Examiner has provided no rebuttal of this showing and has not presented a reasonable basis to believe that the biological material will cease to be available during the enforceable life of the patent. **Without credible reasons or evidence why they would not continue to be readily available, the burden remains with the Examiner to show that claims 27-31 and 73-77 are not enabled.** (MPEP § 2404.01.) Therefore, the Examiner's rejection is deficient.

Even though Applicants believe that the above completely rebuts the Examiner's rejection, Applicants also assert that the relevant VSV strains are sufficiently described in the specification and in the art, at the time of the invention, so that one skilled in the art could make and/or use the relevant VSV strains. For example, Table 11, Figures 14-23, Example 27 and the Sequence Listing of Applicants' specification provide both nucleic acid and amino acid sequence information for viruses that are the subject matter of claims 27-31 and 73-77.

In view of the above, Applicants respectfully request the Examiner to reconsider and withdraw the rejection of claims 27-31 and 73-77 under 35 U.S.C. § 112, first paragraph.

Respectfully submitted,

/Douglas A. Golightly/

Douglas A. Golightly
Agent for Applicants
Registration No. 51,244
240-631-2500 ext. 3342

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